

REMARKS

Claims 1-39 are pending in the instant application. Claims 1-32, 34, and 36-39 are rejected. Claims 33, 35 and 38 are withdrawn from consideration. Applicants appreciate that the last Amendment and Response was partially successful by overcoming the objection to the claims and the rejection under 35 USC 112, first paragraph.

Rejection under 35 USC 103

1. *Reyes et al.*, U.S. Patent 5,994,092 in view of *Ponpipom et al.*, U.S. Patent 4,228,274 and *Crompton et al.*, *Biochem. J.* 70(4):729 (1958)

The Examiner rejects claims 1-4, 21-24, 27-32, 34, 36, 37 and 39 as unpatentable over *Reyes et al.*, U.S. Patent 5,994,092 in view of *Ponpiporn et al.*, U.S. Patent 4,228,274 and *Crompton et al.*, *Biochem. J.* 70(4):729 (1958) as before. In response to previous arguments, the Examiner says that *Crompton et al.* teach using aqueous acetone for recrystallization. Further, the arguments that a purity greater than 99% are achieved must be submitted in a sworn Declaration of an inventor, preferably with experimental results included demonstrating that purity level in order to be persuasive. Evidence of unexpectedly superior results must be persuasive in order to support patentability, and mere attorney argument is not enough for this Examiner.

Applicants respectfully refer the Examiner to the Declaration under 37 C.F.R. 1.132 of Dr. Alfonso Fernandez-Mayoralas Alvarez, submitted herewith. Under oath, Dr. Alvarez provides exactly such sworn testimony with experimental results in paragraph 9. Although crystallization is in fact a common process for purifying sugars, finding the appropriate solvent is not easy. The appropriate solvent depends on the type of molecules and the range of solvents that must be tested and can be very broad. The more customary solvents in sugars tend to be low molecular weight alcohols, water, ethyl acetate, hexane, and their mixtures. Applicants respectfully submit that in a crystallization process, a large number of solvents and mixtures thereof must be tested or screened before arriving at the appropriate solvent to use. In the case of the instant invention, acetone allows obtaining the product desired with a >99% degree of purity, which was not possible with more usual solvents. In Exhibit D a gas chromatogram of the 4-galactosyl-xylose obtained by the process covered by the pending patent application

subject of present declaration, can be shown. Peaks at retention times of 18.70 and 18.92 min correspond to alpha and beta anomers of 4-galactosyl-xylose, respectively. By simply summing the % areas of each peak ($92.566 + 6.540 = 99.106\%$) a purity over 99% is achieved.

In view of the foregoing, Applicants submit that the pending claims are clearly patentable.

2. *Reyes et al.*, U.S. Patent 5,994,092 in view of *Ponpipom et al.*, U.S. Patent 4,228,274 and *Crumpton et al.*, *Biochem. J.* 70(4):729 (1958) further in view of *Wong-Madden et al.*, U.S. Patent 5,770,405 and *Dahmen et al.*, U.S. Patent 4,675,392

The Examiner rejects claims 1, 5, 6 and 16-19 as unpatentable over *Reyes et al.*, U.S. Patent 5,994,092 in view of *Ponpipom et al.*, U.S. Patent 4,228,274 and *Crumpton et al.*, *Biochem. J.* 70(4):729 (1958) further in view of *Wong-Madden et al.*, U.S. Patent 5,770,405 and *Dahmen et al.*, U.S. Patent 4,675,392. The Examiner says that the same solvent system used for a silica gel column would work in an active carbon column absent evidence to the contrary. The Examiner says that arguments that isopropanol/water mixtures require less elution volume than methanol/water or ethanol/water are not persuasive unless supported by evidence (experimental data or sworn statements of an inventor under oath). The Examiner says that the specific recitations of claims 16-19 are mere optimized values. Further, the Examiner says that *Rao et al.* teach extracting fats from a specimen using non-polar chloroform solvent mix but that the samples still contain extractable free sugars that can be isolated by highly polar solvent systems such as 70% ethanol.

Applicants respectfully refer the Examiner again to the Declaration under 37 C.F.R. 1.132 of Dr. Alfonso Fernandez-Mayoralas Alvarez, submitted herewith. Under oath, Dr. Alvarez states that *Wong-Madden et al.*, U.S. Patent 5,770,405 do not use the solvent mixture in a chromatography on active carbon. *Wong-Madden et al.* teach using isopropanol/ethanol/water, but it is to develop a chromatography on silica gel. (Alvarez Declaration, paragraph 10). Further, as explained, *supra*, the instant invention is patentable without even considering the tertiary reference, *Wong-Madden et al.* because of the unexpectedly superior purity rendering the claims patentable over the primary and secondary references.

3. *Reyes et al.*, U.S. Patent 5,994,092 in view of *Ponpipom et al.*, U.S. Patent 4,228,274 and *Crompton et al.*, *Biochem. J.* 70(4):729 (1958) further in view of *Wong-Madden et al.*, U.S. Patent 5,770,405 and *Dahmen et al.*, U.S. Patent 4,675,392 and further in view of *Rao et al.*, *Qual. Plant.-Pl. Fds. Hum. Nutr.* XXVIII 4:293-303 (1979)

The Examiner rejects claims 1 and 7-15 as unpatentable over *Reyes et al.*, U.S. Patent 5,994,092 in view of *Ponpipom et al.*, U.S. Patent 4,228,274 and *Crompton et al.*, *Biochem. J.* 70(4):729 (1958) further in view of *Wong-Madden et al.*, U.S. Patent 5,770,405 and *Dahmen et al.*, U.S. Patent 4,675,392 and further in view of *Rao et al.*, *Qual. Plant.-Pl. Fds. Hum. Nutr.* XXVIII 4:293-303 (1979). The Examiner says that the arguments previously made must be submitted in a sworn Declaration of an inventor, preferably with experimental results included in order to establish unexpected results. According to the Examiner, it would be obvious that one could further extract free sugars with the new 70% ethanol solvent system.

Applicants respectfully refer the Examiner once again to the Declaration under 37 C.F.R. 1.132 of Dr. Alfonso Fernandez-Mayoralas Alvarez, submitted herewith. Under oath, Dr. Alvarez states that active carbon is customarily used to eliminate hydrophobic impurities, but it is not normally used in organic synthesis, for separating monosaccharide and disaccharide mixtures, such as is the case in the above-referenced patent application. The normal course to separate these mixtures is to employ chromatography on a silica gel, on sepharose or others (See, Alvarez Declaration, paragraph 11). The above-referenced patent application describes purifying a mono- and disaccharide mixture using active carbon, which offers the advantage, compared with usual adsorbents (e.g., silica gel or sepharose) of being cheaper. In H. Rotzche, *Journal of Chromatography Library* 1991, 48:104-107 (See, Alvarez Declaration, paragraph 11 and Exhibit E), either structural and geometrical differences between each kind of adsorption matrixes, active carbon in comparison with other column fillings as sepharose, silica gel, etc. are discussed in detail.

The above-referenced patent application describes an isopropanol/water mixture as eluent, as opposed to the more common alcohol/water mixtures such as methanol/water or

ethanol/water. The methods described in the above-referenced patent application thereby provide the advantage of allowing for less elution volume, a significant advantage for industrial production (*See*, Alvarez Declaration, paragraph 12 and Exhibit F). Moreover, ethanol and methanol are more toxic than an isopropanol/water mixture.

Rao *et al.* teach extraction with Soxhlet to extract fats from a specimen of plant origin. Rao *et al.* do not describe using Soxhlet for selectively extracting monosaccharides from a mixture of sugars. (*See*, Alvarez Declaration, paragraph 13).

Further, as explained, *supra*, the instant invention is patentable without even considering the secondary and tertiary references because of the unexpectedly superior purity rendering the claims patentable over the primary references.

4. *Reyes et al.*, U.S. Patent 5,994,092 in view of *Ponpipom et al.*, U.S. Patent 4,228,274, *Crompton et al.*, *Biochem. J.* 70(4):729 (1958), *Dahmen et al.*, U.S. Patent 4,675,392, *Rao et al.*, *Qual. Plant.-Pl. Fds. Hum. Nutr.* XXVIII 4:293-303 (1979) and *Wong-Madden et al.*, U.S. Patent 5,770,405 in further view of *Gabelsberger et al.*, *FEMS Letters* 109(2-3): 131 (1993), *Fujimoto et al.*, *Glycoconjugate Journal* 15:155 (1998) and *Yoshitake et al.*, *Eur. J. Biochem.* 101:395 (1979).

The Examiner rejects claims 25 and 26 as unpatentable over this combination. The Examiner says that the previous arguments (that when cosolvents are added to the reaction medium the yields are lower) must be submitted in a sworn Declaration of an inventor, preferably with experimental results included in order to establish unexpected results. According to the Examiner, it would have been obvious to one of ordinary skill in the art to use any of these three solvents in the phosphate buffer of Reyes *et al.* Further, the amounts allegedly recited represent mere optimization parameters according to the Examiner.

Applicants respectfully refer the Examiner once again to the Declaration under 37 C.F.R. 1.132 of Dr. Alfonso Fernandez-Mayoralas Alvarez, submitted herewith. In view of the explanations under sworn testimony, particularly those found in paragraphs 9-13, the following are clear:

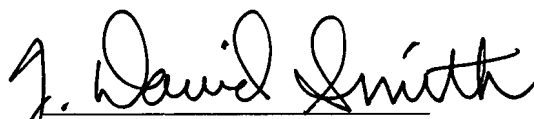
1. Purity greater than 99% is achieved;
2. The same solvent system used for a silica gel column would not work in an active carbon column; and
3. Isopropanol/water mixtures require less elution volume than methanol/water or ethanol/water.

In short, the Examiner does not refute any of Applicants' earlier arguments. Now Applicants provide the factual bases for these arguments under oath signed by an inventor under 37 C.F.R. 1.312. Further, Applicants submit additional experimental data to support the conclusions as to purity. As such, Applicants submit that the issue of the separate patentability of the cosolvent media of claims 25 and 26 is moot in view of the failure of the remaining prior art to render any of the claims obvious.

CONCLUSION

Entry of the foregoing remarks into the record of the above identified application is respectfully requested. It is believed that all of the claims are in condition for allowance. If any issue can be resolved telephonically, the Examiner is requested to call the undersigned at the phone number provided.

Respectfully submitted,


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